REMARKS

Reconsideration and withdrawal of any rejection of the application, and allowance of the claims, especially in view of the remarks made herein, are respectfully requested.

Claims 11-26 are pending in this application. Claims 14 and 15 are withdrawn from further consideration. Claims 11-13 and 16-26 are rejected. Claim 13 is amended herein. It is submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§101, 102, 103 and 112. The amendments to the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments to the claims are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support for the claim amendments is found within the specification. No new matter is added.

The Objection is Overcome

Claim 13 is objected to because of the use of the abbreviations in parentheticals: "(DAMGO)", "(DPDPE)", "(DSLET)" in the claim. The claim has been amended to remove the abbreviations in parentheticals.

It is respectfully requested that the objection to claim 13 be withdrawn since the appropriate corrections have been made.

The Rejection Under 35 U.S.C. § 112 is Overcome

Claims 13 was rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. It is respectfully submitted that the pending claims are definite. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112 is respectfully requested.

Submitted with this response under Tab A are copies of pages from a chemical catalog known to those skilled in the art, listing U50,488 and U69,593 and their corresponding chemical names.

The Rejections Under 35 U.S.C. § 103 is Overcome

Claims 11-13 and 16-26 were rejected under 35 U.S.C. § 103, as being unpatentable over U.S. Patent No. 5,948,389 to Stein (the "Stein patent") and Saito et. al. ("Saito").

The present invention is directed to methods of use of topical pharmaceutical compositions, formulated with at least one local anesthetic and at least one opioid analgesic, and to methods of providing pain relief to a subject through topical administration of the composition in an amount and a duration sufficient to synergistically potentiate an antinociceptive response. Topical administration of the inventive composition advantageously results in insubstantial, if any, systemic absorption.

For an obviousness rejection under § 103 to be proper, both the suggestion of the claimed invention and the expectation of success must be found in the prior art. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). The cited references, taken alone or together, fail to provide a suggestion, much less an expectation, of synergistic potentiation between the peripheral pathways that mediate antinociceptive responses.

Prior to the teaching in the instant application, the importance of peripheral mechanisms in the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to be mediated through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. The synergistic potentiation of pain relief that occurs in the periphery when opioid analgesics are administered together with local anesthetics was unexpected given the state of the art.

The Saito reference does not teach or suggest the invention of the instant application. At best, Saito continues to emphasize the views of those skilled in the art—that analgesic actions are mediated through the central nervous system. Saito teaches the intrathecal administration (via cerebrospinal fluid) of an opioid in combination with an anesthetic whereby such a co-administration leads to a synergistic analgesic effect. However, this reference simply reflects the views of those skilled in the art at the time of filing of the application, namely that analgesia is mediated through the central nervous system. Nowhere in Saito is it suggested that combinations of analgesics and local anesthetics can synergistically stimulate peripheral sites.

Similarly, the Stein patent fails to teach or suggest the present invention. The Stein patent is directed to topical administration of hyperosmolar solutions of opioids or anesthetics (or mixes thereof) such that the drugs first pass into non-inflamed tissue in order to reach inflamed tissue. Importantly, the Stein patent does not teach or suggest that there is a synergistic effect between opioid analgesics and local anesthetics at peripheral sites, which is the unexpected result of the instant invention. In fact, the Stein patent does not teach that use of two agents in combination would be any better than the use of a single agent alone, much less synergistic. This marks a clear distinction between the Stein patent and the instant invention.

The claimed methods are directed to synergistic potentiation of antinociceptive responses at peripheral sites. Synergistic potentiation at peripheral sites was unknown in the art, as evidenced by the cited references and their representative failure to fill this void. Teaching or suggestion for synergistic potentiation at peripheral sites is simply absent from the cited references and the art as a whole. Therefore, motivation for the combination of the cited references comes only from the Examiner's impermissible use of hindsight reconstruction.[1] Synergistic potentiation at peripheral sites is a missing link between the cited references, found only in the teaching of the instant application. Thus, impermissible hindsight reconstruction is the only means by which cited references were selected, combined and relied upon by the Examiner.

The initial burden is on the Examiner to establish that there is some suggestion of the desirability of doing what the inventor has done, some suggestion in the art to do so and an expectation of success. These requirements have not been met. Reconsideration and withdrawal of the rejections under 35 U.S.C § 103 are respectfully requested.

[1] Hindsight—based on the Applicants' own success as disclosed and claimed in the instant application—is not a justifiable basis on which to propose that the ultimate achievement of the present invention would have been obvious at the time the invention was made. *In re Fine*, 5 U.S.P.Q.2d 1596, 1599, 1600 (Fed. Cir. 1988) (stating that one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to arrive at the claimed invention).

CONCLUSION

Applicants believe that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Attorneys For Applicants

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APPENDIX 1: MARKED-UP VERSION OF AMENDMENTS

The marked-up amendments have been highlighted for the Examiner's convenience in entering the amendments to the claims.

In the Claims:

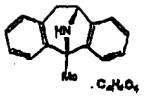
13. (Amended) The method according to claim 11, wherein the opioid is selected from the group consisting of ethylmorphine, hydromorphine, morphine, oxymorphone, codeine, levorphanol, oxycodone, pentazocine, propoxyphene, fentanyl, sufentanil, lofentanil, morphine-6-glucuronide and buprenorphine, methadone, etorphine, [D-Ala^2,MePhe^4,Gly(ol)^5]enkephalin **[(DAMGO)]**, butorphanol, nalorphine, nalbuphine, naloxone benzoylhydrazone, bremazocine, ethylketocyclazocine, **trans-(-)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide [U50,488]**, **(5-alpha,7-alpha,8-beta)-(+)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro(4,5)dec-8-yl]-benzeneacetamide [U69,593]**, spiradoline, naltrindole, [D-Pen^2,D-Pen^5]enkephalin **[(DPDPE)]**, [D-Ala^2,Glu^4]deltorphin, **[and]** [D-Ser^2,Leu^5]enkephalin-Thr^6 **[(DSLET)], and their mixtures and physiologically acceptable salts thereof**.

Catalog Number	Product	Unit	Unit Price US Dollar

0924 (+)-MK 801 maleate — 10 mg: 25.00; 50 mg: 112.00

Dizocilpine / (5R,10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d] cycloheptan-5,10-imine

M.W. 337.37
Store at RT
Soluble to 10 mM in water
[77086-22-7]



A potent, selective and non-competitive NMDA receptor antagonist. MK 801 acts by binding to a site located within the NMDA associated ion channel and thus prevents Ca^{2+} flux. An effective anticonvulsant agent in several animal models.[1]

Wong *et al* (1986) The anticonvulsant MK 801 is a potent NMDA antagonist. Proc.Natl.Acad.Sci.USA *83* 7104. Gill *et al* (1991) The neuroprotective action of dizocilpine (MK-801) in rat middle cerebral artery occlusion model of focal ischaemia. Br.J.Pharmacol. *103* 2030. Hatfield *et al* (1992) The dose-response relationship and therapeutic window for dizocilpine (MK-801) in a rat focal ischaemia model. Eur.J.Pharmacol. *219* 1. Zajaczkowski *et al* (1997) Uncompetitive NMDA receptor antagonists attenuate NMDA-induced impairment of passive avoidance learning and LTP. Neuropharmacology. *36* 961.

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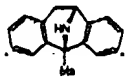
☢ **Available in radiolabeled form - see R924**

R924 [^{3}H]-(+)-MK 801 — 250 µCi / 9.25 MBq: 795.00; 1 mCi / 37 MBq: 1590.00

[^{3}H]-Dizocilpine / (5R,10S)-(+)-5-Methyl-[3,7-^{3}H]-10,11-dihydro-5H-dibenzo[a,d] cycloheptan-5,10-imine

NEW ☢ Unlabeled M.W. 221.30
Specific activity: 15-40 Ci/mmol (555-1480 GBq/mmol)
Solvent: ethanol:water (1:1)
Shipped in dry ice



Potent non-competitive NMDA receptor antagonist radioligand, which binds to the activated form of the receptor complex (the K_d value for binding to rat cerebral cortical membranes is approximately 6 nM). Binding is allosterically modulated by Mg^{2+}, glutamate and polyamines.

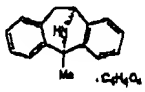
Wong *et al* (1988) [^{3}H]MK-801 labels a site on the N-methyl-D-aspartate receptor channel complex in rat brain membranes. J.Neurochem. *50* 274. Javitt and Zukin (1989) Interaction of [^{3}H]MK-801 with multiple states of the N-methyl-D-aspartate receptor complex of rat brain. Proc.Natl.Acad.Sci.USA *86* 740. Murray *et al* (2000) Modulation of [^{3}H]MK-801 binding to NMDA receptors *in vivo* and *in vitro*. Eur.J.Pharmacol. *397* 253.

(Radioactive license required – please send with first radiochemical order)

0955 (-)-MK 801 maleate — 10 mg: 17.00; 50 mg: 76.00

(5S,10R)-(-)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d] cycloheptan-5,10-imine

M.W. 337.37
Store at RT
Soluble in water
[77086-19-2]



Less active enantiomer. See catalog number 0924 for further information.

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MISCELLANEOUS COMPOUNDS

DEA CODE	SCHEDULE	DRUG NAME
9624	1	Etonitazene
9624	1	Etonitazene HCl
NOCD	0	N-Nordiphenhydramine HCl
NOCD	0	N,N-Dinordiphenhydramine HCl
NOCD	0	trans-(dl)-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]benzeneacetamide methanesulfonate hydrate
(U50,488H, Upjohn)		
NOCD	0	(5-alpha,7-alpha, 8-beta)-(+)-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro(4,5)dec-8-yl]-benzeneacetamide (U69,593, Upjohn)
NOCD	0	Norbinaltorphimine (norBNI) dihydrochloride
NOCD	0	1-[2-(Diphenylmethoxy)ethyl]-4-(3-phenyl-2-propenyl)piperazine dihydrochloride (GBR 12783)
NOCD	0	(dl)-6-Chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro[1H] -3-benzazepine HBr
NOCD	0	(dl)-6-Chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro[1H] -3-benzazepine HCl
NOCD	0	(dl)-1-(2-Bromo-4,5-dimethoxybenzyl)-7-hydroxy -6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (A69024) HBr
NOCD	0	(dl)-5-(Aminocarbonyl)-10,11-dihydro-5H -dibenzo[a,d]cycloheptene-5,10-imine(ADCI) HCl
NOCD	0	(3S)-(+)-2,3-Dimethyl-6,7-methylenedioxytetrahydroisoquinoline HCl
NOCD	0	Mesocarb
NOCD	0	trans-2,5-Dimethylpiperazinecarboxylate (SNC 80)